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## ***MONITORING ANTHRAX VACCINE SAFETY IN U.S. MILITARY SERVICE MEMBERS ON ACTIVE DUTY: SURVEILLANCE OF HOSPITALIZATIONS IN TEMPORAL ASSOCIATION WITH IMMUNIZATION, 1998***

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# **MONITORING ANTHRAX VACCINE SAFETY IN U.S. MILITARY SERVICE MEMBERS ON ACTIVE DUTY: SURVEILLANCE OF HOSPITALIZATIONS IN TEMPORAL ASSOCIATION WITH IMMUNIZATION, 1998**

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## **ABSTRACT**

We studied military medical hospitalizations for possible temporal associations with anthrax immunization in U.S. military personnel on active duty in 1998. Anthrax immunization, demographic, and hospitalization data were linked and analyzed using Cox proportional hazards modeling for hospitalization within 42 days of an anthrax vaccine dose. Discharge diagnoses were aggregated into 14 International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic categories. Approximately 11% of active-duty personnel received one or more doses of anthrax vaccine during 1998; those anthrax immunized were more likely to be younger and male. Lower hospitalization rates were observed in the anthrax-immunized, across doses and diagnostic categories. Adjusted risk ratios for hospitalization by diagnostic category suggests that anthrax-immunized active-duty service members were at equal or lesser risk of hospitalization than the nonimmunized.

## **INTRODUCTION**

The value of anthrax as a biological weapon stems from its high stability in spore form, from the relative absence of natural immunity in industrialized nations, and from the severity of disease in its inhalation form.<sup>1-3</sup> The threat posed by anthrax to the U.S. military prompted the Secretary of Defense, in December 1997, to order a mandated program for anthrax immunization of all U.S. military personnel. This program is currently being implemented.<sup>1</sup>

Phase I, an accelerated immunization program for personnel who were already deployed in Southwest Asia, began in March 1998, as tensions with Iraq over United Nations weapons inspections increased. In August of the same year, the program was extended to personnel assigned or rotating to high threat areas.<sup>1</sup> Ensuing phases of the immunization program will begin in subsequent years.

As of April 12, 2000, a total of 425,976 service members had received 1,620,793 anthrax vaccine doses. Approximately 500 service members have

refused anthrax vaccine immunization, despite the administrative or disciplinary action that may result.<sup>2</sup> Concerns that there may be long-term severe and/or permanent adverse effects to immunization have been among the reasons for refusing immunization.<sup>2</sup> In response to these concerns, we initiated a study to monitor anthrax vaccine safety. The study uses available U.S. Department of Defense (DoD) data to assess hospitalizations that occur in close temporal proximity to anthrax immunization. We report here on findings for calendar year 1998.

## MATERIALS AND METHODS

Personal identifying information was used for matching and linking immunization, demographic, and hospitalization data during data analysis. Such identifying information was kept in secure conditions designed to assure confidentiality and privacy. All identifying information was disassociated and deleted from the analytical data set once linking was complete.

### Anthrax Immunization Status Data

Anthrax immunization status was determined from records maintained by the Defense Eligibility Enrollment Reporting System (DEERS) at the Defense Manpower Data Center, Seaside, California. Anthrax immunization data for 1998 on record as of December 31, 1999, were obtained. Anthrax dose sequence number and date of dose administration, among other variables, were used in these analyses.

### Demographic Data

Demographic data for service members were also obtained from DEERS. Data for all U.S. military personnel on active duty for all or part of 1998, and on record as of December 31, 1999, were used. DEERS contains data on changes of military assignment, contingency deployments, as well as on dates of accession to and/or

discharge from military service, among others.

### Hospitalization data

A database containing the Standard Inpatient Data Record (SIDR) for all hospitalizations at military medical treatment facilities (MTFs) is maintained at Fort Detrick, Maryland. This database contains up to 8 hospitalization discharge diagnoses coded in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. Other information available in this database includes length of hospital stay, dates of admission, and dates of discharge.

A subject experienced a hospitalization event if he or she was discharged from an MTF with a diagnosis classified under one of 14 targeted ICD-9-CM diagnostic categories (Table I). Anthrax-immunized service members experienced a hospitalization event if it occurred within 42 days following an anthrax vaccine dose. This 0- to 42-day time window is consistent with conventions described in the literature.<sup>4-6</sup> Nonimmunized service members experienced an event if they were hospitalized any time between January 1 and December 31, 1998.

### Objective

We studied military hospitalizations in temporal association with anthrax immunization in U.S. military personnel on active duty in 1998. Adjusted risk ratios (ARRs) with 95 % confidence intervals (CIs) for hospitalization comparing anthrax immunized with nonimmunized service members were computed to study this association.

### Statistical analysis

Chi-square tests and *t* tests for associations were used to determine possible predictors of hospitalization. Variables with *p* values of #0.15 obtained from these tests were included in subsequent model analyses. A multivariable Cox proportional hazards

model was used with a manual, backward, stepwise model-building process to compare risk for hospitalization between anthrax-immunized and nonimmunized service members. Data management and statistical analysis were performed using SAS Version 6 software (SAS Institute, Cary, NC).

Person-years of observation were counted for anthrax immunized, within the 42-day window, from the date of immunization until whichever of the following occurred first: (a) the date of first admission, (b) the date of next anthrax vaccine dose, (c) the date of separation from military service, or (d) December 31, 1998. Person-years for nonimmunized service members were calculated from January 1, 1998, until whichever of the following occurred first: (a) the date of first admission, (b) the date of separation from military service, or (c) December 31, 1998. Subsequent hospitalizations within the same diagnostic category for any service member, in either group, were not counted as events.

The following covariates were included in the final model to adjust for contributing effects: prior hospitalization between January 1 and December 31, 1997; gender; age (quartile groupings: 16-21, 22-26, 27-33, and  $\geq 34$  years); marital status (married, not married); and race/ethnicity (white, black, hispanic, other). Additional covariates included paygrade (enlisted, warrant officer, commissioned officer), duty occupational category (divided into 10 major groupings per DoD Occupational Conversion Index<sup>7</sup>), branch of service, deployment status (deployed prior to January 1, 1998, deployed during study period, deployed during study period, and deployed four or more times during career), and date of separation from active-duty military service.

## RESULTS

### Demographic Profiles

The demographic characteristics of anthrax-immunized service members were compared with the entire active-duty population (Table II). There was a slightly greater proportion of men among the anthrax immunized in 1998, and they were also

younger than the active-duty population as a whole.

### Anthrax Immunization Status

DoD-wide, 11.3 % of active-duty service members had received at least one dose of anthrax vaccine in 1998. There was a generally proportionate representation of Army, Navy, Air Force, and Marine Corps personnel (Table III).

### Hospitalizations

For anthrax-immunized service members, there were 719 unique hospitalizations within 14 ICD-9-CM diagnostic categories during 28,619 person-years of observation. Among the nonimmunized, there were 47,391 hospitalizations during 1,248,332 person-years of observation. Table I provides a summary of ICD-9-CM diagnostic categories and the abbreviations for the categories used in Figures 1 and 2.

Anthrax-immunized service members had lower rates of hospitalization across doses and diagnostic categories. All point estimates of ARR by diagnostic category were less than 1.0. For 7 of 14 categories (Fig. 2), the 95 % CI around ARR included 1.0. The 95 % CI for the 7 other ICD-9-CM diagnostic categories did not include 1.0, suggesting that immunized active-duty service members were significantly less likely to be hospitalized for conditions in these diagnostic categories than their nonimmunized counterparts (Fig. 2).

## DISCUSSION

We report on data from the first year of a multi-year study designed to monitor anthrax vaccine safety in U.S. military service members on active duty. Through surveillance of hospitalizations in MTFs, we have sought to monitor ICD-9-CM category-specific risks associated with anthrax immunization. These data refer to only calendar year 1998.

In our results, anthrax immunization was not associated with an increased risk for

hospitalization within 42 days following immunization. Immunized service members were at equal or lesser risk for hospitalization than nonimmunized service members during the period of observation. Nonetheless, this study had a number of limitations.

First, there is a potential confounder that may explain some of our results. Figure 2 shows that the point estimates for the ARR in anthrax-immunized personnel are lower across all diagnostic categories. Some part of this effect could be due to the fact that a majority of those immunized in 1998 were likely among the forward deployed or deployable, among those stationed overseas, and/or among those stationed in high threat areas. If selection for deployment is biased in favor of the healthier service member, it may well be expressed among the deployed and/or deployable as a decreased risk of hospitalization, particularly for routine or nonurgent hospitalizations that may be deferred until the end of deployment. This effect, thought to be transient, was seen in hospitalizations among service members deployed to the Gulf War in 1991.<sup>8</sup> We attempted to control for this "healthy deployment effect" by including the prior hospitalization covariate in our explanatory model. Additional methods for adjusting for this effect are being investigated.

Second, although personnel on active duty are generally required to obtain their health care at an MTF, some hospitalizations of service members on active duty occur in non-DoD facilities, mainly through DoD-sponsored health plans (TriCare and CHAMPUS). This is thought to be infrequent, especially for service-related events. Nonetheless, we are

currently planning to incorporate data from hospitalizations in non-MTFs that are billed to TriCare and CHAMPUS health plans into future years of our multi-year study. Non-MTF hospitalizations may also be more likely among service members in units deployed to areas where MTFs are few in number or far away in distance, such as in Southwest Asia. This may also explain some of the apparent decreased risk for hospitalization among anthrax-immunized personnel. Most of these cases should eventually appear in SIDR hospitalization databases; they would likely be medically evacuated back to the United States or to the nearest MTF as soon as their condition stabilized, and rehospitalized for further evaluation and treatment.

Finally, as previously mentioned, these data are from the first year of a multi-year study, and they reflect only the first year of the DoD's current anthrax immunization program. As a result, anthrax-immunized service members contributed less than 3% of the total observation time contributed by all service members on active duty, and only slightly more than 11 % had received at least one dose of anthrax vaccine.

The number of person-years of observation in the anthrax immunized should increase rapidly as additional years of data are obtained. This will provide the study with greater statistical power, permitting examination of potential associations between anthrax vaccine and specific diagnoses that have been alleged or found to be associated with the use of vaccines, such as serum sickness, other hypersensitivity reactions, and Guillain-Barré syndrome.<sup>6</sup>

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This research has been conducted in compliance with all applicable Federal Regulations governing the protection of human subjects in research.

## REFERENCES

1. Mazzuchi JF, Claypool RG, Hyams KC, Trump D, Riddle JR, Patterson RE, Bailey S: Protecting U.S. military forces: a national obligation. *Aviat Space Environ Med* 2000;71:260-5.
2. Sato PA, Ryan M, Gray GC, Hoffman KJ, Costello CN, Wassermann GM, Rubertone MV, Stanek, SA, Grabenstein, JD, Riddle JR, Trump D: Surveillance for adverse events associated with anthrax vaccination-U.S. Department of Defense, 1998-2000. *MMWR* 2000;49:341-5.
3. Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Hauer J, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russel PK, Tonat K: Anthrax as a biological weapon. *JAMA* 1999;281:1735-45.
4. Griffin M, Ray W, Livengood J, Schaffner W. Risk of Sudden Infant Death Syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *New Engl J Med* 1988;319:618-23.
5. Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Vadheim CM, Marcy SM, Ward JI, Wise RP, Wassilak SG, Hadler SC, Vaccine Safety Datalink Team: Vaccine safety datalink project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997;99:765-73.
6. Chen RT: Safety of Vaccines. In: *Vaccines*, pp 1144-63. Edited by Plotkin SA, Orenstein WA. Philadelphia: PA, WB Saunders, 1999.
7. Office of the Assistant Secretary of Defense for Personnel and Readiness: *Occupational Conversion Index*. . Washington, DC: U.S. Department of Defense; 1993.
8. Gray GC, Coate BD, Anderson CM, Kang HK, Berg SW, Wignall FS, Knoke JD, Barrett-Connor E: The postwar hospitalization experience of US veterans of the Persian Gulf War. *N Engl J Med* 1996;335:1505-13.

TABLE I. Summary Of ICD-9-CM Diagnostic Categories Used In Study Analysis

ICD-9-CM Diagnostic Category	ICD-9-CM Codes in Category	Abbreviations Used in Figures 1 and 2
Infectious and parasitic diseases	001-139	Infectious
Neoplasms	140-239	Neoplasms
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	Endocrine
Diseases of the blood and blood forming organs	280-289	Blood
Mental disorders	290-319	Mental
Diseases of the nervous system and sense organs	320-389	Nervous
Diseases of the circulatory system	390-459	Circulatory
Diseases of the respiratory system	460-519	Respiratory
Diseases of the digestive system	520-579	Digestive
Diseases of the genitourinary system	580-629	Genitourinary
Diseases of the skin and subcutaneous tissue	680-709	Skin
Diseases of the musculoskeletal system and connective tissue	710-739	Musculoskeletal
Symptoms, signs, and ill-defined conditions	780-799	Ill-defined
Injury and poisoning	800-999	Injury

TABLE II. Demographic And Military Profile Of All Service Members On Active Duty Compared With Those Anthrax Immunized, 1998

	All Active-Duty Personnel		Anthrax-Immunized	
	Number	%	Number	%
<b>Gender</b>				
Male	1,210,251	86.0	144,683	90.8
Female	196,779	14.0	14,691	9.2
<b>Age, years</b>				
#19	164,299	11.7	14,846	9.3
20-24	409,959	29.1	56,560	35.5
25-29	285,932	20.3	33,750	21.2
30-34	228,707	16.2	26,054	16.3
35-39	199,347	14.2	19,574	12.3
40-44	83,425	5.9	6,512	4.1
45-49	28,032	2.0	1,741	1.1
≥50	8,017	0.6	349	0.2
<b>Race/ethnicity</b>				
White	910,123	68.8	103,728	69.7
Black	277,654	21.0	32,750	22.0
Hispanic	102,944	7.8	12,076	8.1
Other	31,929	2.4	230	0.2
<b>Service</b>				
Army	475,582	33.8	60,761	38.1
Navy	366,867	26.1	36,652	23.0
Air Force	359,853	25.6	43,696	27.4
Marine Corps	171,199	12.2	18,277	11.5
Other	34,217	2.4	0	0.0
<b>Military paygrade</b>				
Enlisted	880,090	63.1	101,480	64.1
Officer	515,271	36.9	56,867	35.9

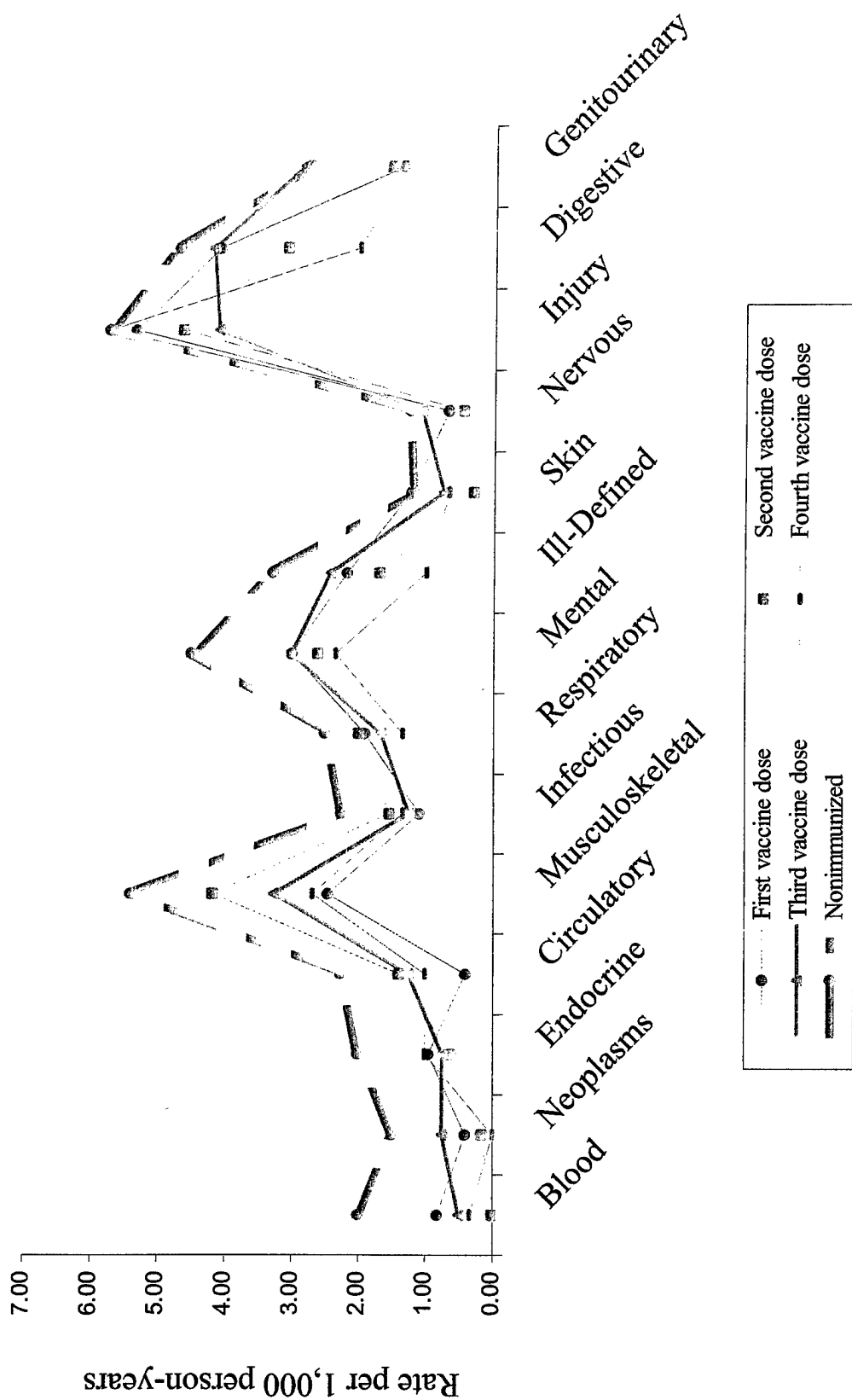


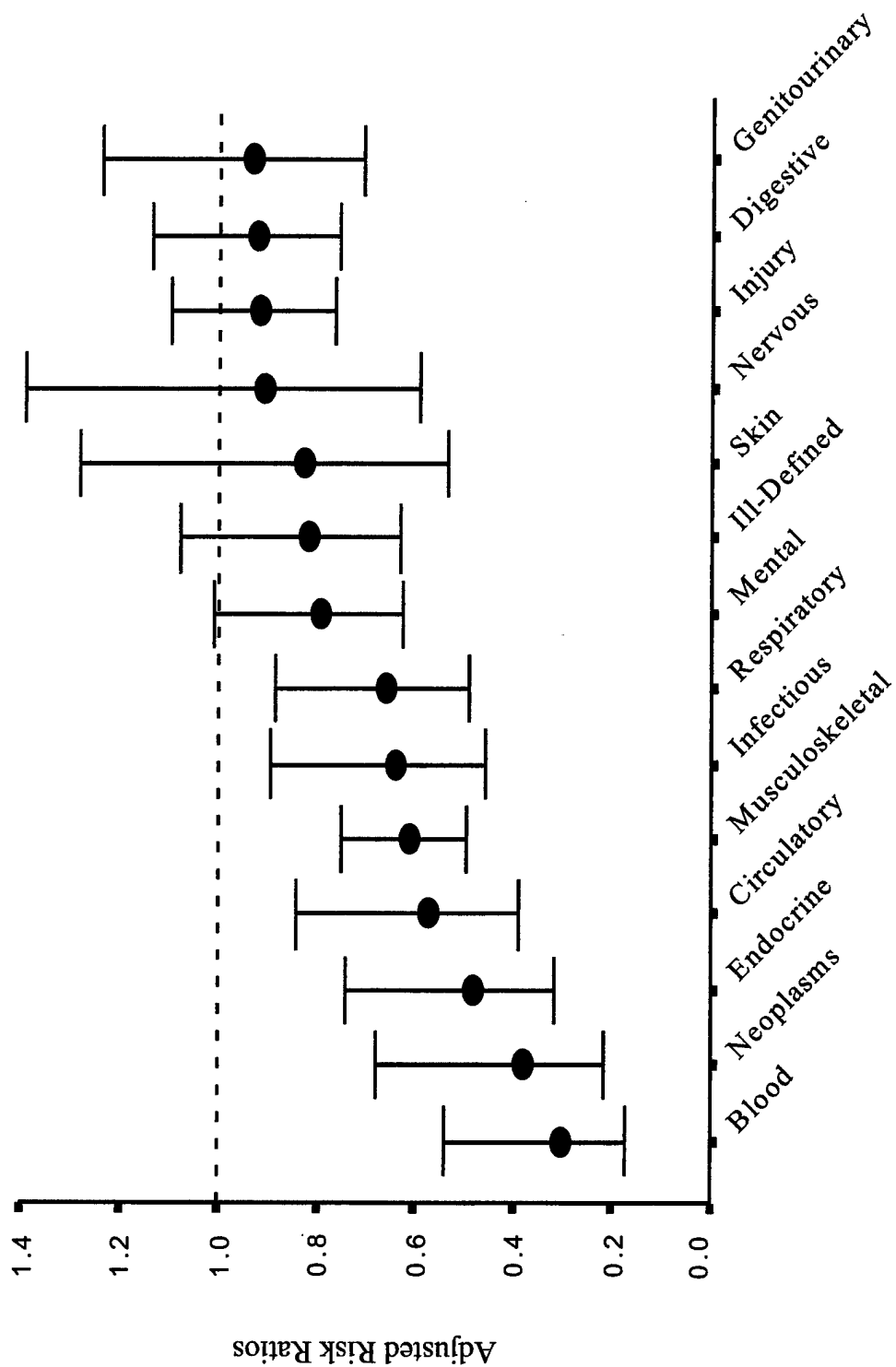
TABLE III. Anthrax Immunization Status By Service And By Number Of Anthrax Vaccine Doses Given, 1998

Number of Doses	Total		Army		Navy		Air Force		Marine Corps		Other	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
E1	159,386	11.32	60,761	12.78	36,652	9.99	43,696	12.14	18,277	10.68	0	0.00
E2	142,004	10.09	53,016	11.15	32,516	8.86	40,661	11.30	15,811	9.24	0	0.00
E3	121,591	8.64	44,201	9.29	28,465	7.76	36,692	10.20	12,233	7.15	0	0.00
E4	28,756	2.04	9,969	2.10	6,237	1.70	10,631	2.95	1,919	1.12	0	0.00
E5	487	0.03	173	0.04	31	0.01	136	0.04	147	0.09	0	0.00
E6	203	0.01	69	0.01	15	0.00	23	0.01	96	0.06	0	0.00
Booster doses	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Zero doses	1,248,332	88.68	414,821	87.22	330,215	90.01	316,157	87.86	152,922	89.32	34,217	100.00
All active duty	1,407,718		475,582		366,867		359,853		171,199		34,217	

Fig.1. Hospitalization rates by ICD-9-CM diagnostic category and anthrax vaccine dose, 1998. U.S. military service members on active duty.

Fig. 2. Adjusted risk ratios for hospitalization with 95% confidence intervals, by ICD-9-CM diagnostic category, 1998. U.S. military service members on active duty.





## REPORT DOCUMENTATION PAGE

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